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Quaternary stereocentres via catalytic enantioconvergent nucleophilic substitution reactions of tertiary alkyl halides by alkenylmetal reagents

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Abstract

The development of efficient methods, particularly catalytic and enantioselective processes, for the construction of all-carbon quaternary stereocentres is an important (and difficult) challenge in organic synthesis, due to the occurrence of this motif in a range of bioactive molecules. One conceptually straightforward and potentially versatile approach is the catalytic enantioconvergent substitution reaction of a readily available racemic tertiary alkyl electrophile by an organometallic nucleophile; however, examples of such processes are rare. In this report, we demonstrate that a nickel-based chiral catalyst achieves enantioconvergent couplings of a variety of tertiary electrophiles (cyclic and acyclic α-halocarbonyl compounds) with alkenylmetal nucleophiles to form quaternary stereocentres with good yield and enantioselectivity under mild conditions in the presence of a range of functional groups. These couplings, which likely proceed via a radical pathway, provide access to an array of useful families of organic compounds, including intermediates in the total synthesis of two natural products, (−)-eburnamonine and madindoline A.

Because carbon atoms that bear four carbon substituents are found in a wide variety of natural products and other bioactive molecules (e.g., morphine and Symbicort, among the top 100 small-molecule pharmaceuticals by retail sales in 2018, 10% include a quaternary stereocentre: https://njardarson.lab.arizona.edu/content/top-pharmaceuticals-poster), substantial attention has been devoted to the development of methods for the synthesis of quaternary carbons.[1–3] The construction of such highly substituted centres can itself be challenging, due to a steric impediment to bond formation. Controlling enantioselectivity, when the carbon is stereogenic, adds another dimension to the challenge. Finally, dictating

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Author Contributions

Z.W. and Z.-P.Y. performed all experiments. Z.W. and G.C.F. wrote the manuscript. All authors contributed to the analysis and the interpretation of the results.

Competing Interests Statement

The authors declare no competing interests.

Data Availability Statement: The data that support the findings of this study are available within the paper, within the Supplementary Information (experimental procedures and characterization data). Crystallographic data for the structures reported in this Article have been deposited at the Cambridge Crystallographic Data Centre, under the deposition numbers CCDC 1958912 (**13**), 1958913 (**81**), and 1965146 (**80**). Copies of the data can be obtained free of charge via https://www.ccdc.cam.ac.uk/structures/.

stereochemistry through the use of a chiral catalyst, rather than relying on substrate control or a stoichiometric chiral reagent, further elevates the challenge.[4,5]

While important progress has been described in achieving the catalytic asymmetric synthesis of quaternary stereocentres, the available methods allow access to only a small subset of the structures of interest.[1–5] The catalytic enantioconvergent substitution of readily available racemic tertiary (all carbon substituents) alkyl electrophiles by carbon nucleophiles represents a potentially versatile strategy for addressing this challenge, and some noteworthy advances have been reported that proceed via heterolytic cleavage of the C–X bond (X = leaving group; Figure 1), including several S_N1 reactions[6–9] and couplings of allyl electrophiles,[10–13] propargyl electrophiles,[14,15] and 3-halooxindoles.[16–19]

A complementary pathway for achieving catalytic enantioconvergent substitution reactions of tertiary alkyl electrophiles is to exploit homolytic, rather than heterolytic, cleavage of the C–X bond of the electrophile (Figure 1); relative to tertiary carbocations (S_N1 reactions), tertiary radicals can often be generated under milder conditions and are typically less prone to undesirable side reactions such as the loss of a proton to form an olefin, as well as rearrangements. A number of reports have established that transition metals can catalyze enantioconvergent nucleophilic substitutions of racemic secondary alkyl electrophiles via a radical pathway.[20–23] The corresponding couplings of tertiary electrophiles, to control quaternary stereocentres with good enantioselectivity, has been studied with partners such as an olefin/hydrosilane[24] or an *N*-aryl-α-amino acid[25] or via catalysis by a Lewis acid (Figure 1),[26] but the use of organometallic nucleophiles is underexplored. A recent study by Zhang, published after the completion of our study, gives an example of this type of reaction, reporting a nickel-catalyzed method for the enantioconvergent coupling of epoxides with alkenylboronic acids.[27]

In this report, we demonstrate that a chiral nickel catalyst can achieve enantioconvergent substitution reactions of racemic tertiary alkyl electrophiles by organometallic nucleophiles to provide quaternary stereocentres with good enantioselectivity; specifically, we establish that an array of tertiary α-halocarbonyl compounds, both cyclic and acyclic, couple with alkenylzirconium reagents under mild conditions (Figure 1b). We further illustrate that the coupling products can be transformed into diverse and useful families of enantioenriched molecules, enabling the formal total synthesis of two bioactive natural products, (−)-eburnamonine and madindoline A.

Results and discussion

The development of efficient methods for the enantioselective synthesis of carbonyl compounds that bear a quaternary stereocentre at the α position is an important objective in organic synthesis, due to the presence of this subunit in a variety of natural and unnatural bioactive compounds (e.g., estrone and paclitaxel). Catalytic asymmetric processes for the construction of such stereocentres are dominated by reactions wherein the α-carbon serves as a nucleophile (e.g., an enolate or an enol ether), coupling with an electrophile.[28,29] In contrast, the umpolung approach, wherein the α-carbon serves as an electrophile, has rarely

been explored, with the exception of couplings of 3-halooxindoles, α-iodolactones, and α-spiroepoxyoxindoles.[16–19,26,27]

Cyclic electrophiles.

Alkenylzirconium reagents have proved to be useful nucleophiles in metal-catalyzed couplings,[30] due in part to their readily availability (reaction of commercially available Schwartz's reagent with alkynes), their ability to transmetalate to a catalyst under mild conditions without the need for a Lewis-basic activator (in contrast to typical Suzuki and Hiyama reactions), and their good functional group compatibility. Upon investigating an array of parameters, we determined that a chiral nickel/pyridine-oxazoline catalyst can achieve the enantioconvergent coupling of a racemic tertiary α-halocarbonyl compound with an alkenylzirconium reagent with very good yield and enantioselectivity at room temperature (Table 1, entry 1); both $NiCl_2$·glyme and the chiral ligand (**L1**) are commercially available. Pyrrolidinones that bear a quaternary stereocentre in the 3 position have proved to be versatile intermediates in the total synthesis of natural products.[31]

Essentially no coupling is observed in the absence of $NiCl_2$·glyme (Table 1, entry 2), whereas a low yield of racemic product is obtained if the chiral ligand (**L1**) is omitted (Table 1, entry 3). Other families of chiral ligands that have proved useful for enantioconvergent nickel-catalyzed couplings of secondary electrophiles are not effective for this tertiary electrophile under these conditions (Table 1, entries 4–6).[20]

From a practical point of view, it is noteworthy that the yield of the coupling product is only modestly diminished, and the enantiomeric excess is unaffected, if a 1.0:1.0 ratio of electrophile:nucleophile is used, the reaction is run for a shorter time, or a trace of water or air is present (Table 1, entries 7–10). The illustrated conditions employ 0.5 mol% nickel, which is less than any previous nickel-catalyzed enantioconvergent coupling of alkyl electrophiles of which we are aware (previous minimum: 3 mol%[32]). Interestingly, an even lower loading of nickel can be used, without any loss in enantioselectivity, leading to a turnover number as high as ~1600 (Table 1, entries 11–13; in the case of a gram-scale coupling (1.1 g of product) in the presence of 0.05 mol% nickel, carbon–carbon bond formation proceeds in 69% yield and 96% e.e., corresponding to a turnover number of ~1400; for additional data, see Section III of the Supplementary Information). The corresponding alkyl chloride couples slowly under the same conditions, but with comparable enantioselectivity (Table 1, entry 14; ~8 turnovers after 24 h). Under our standard conditions, a corresponding alkenylmagnesium, -zinc. -boron, and -silicon reagent afford low (<5%) yield and/or low (<5%) e.e..

We next examined the scope of this method for the catalytic asymmetric synthesis of quaternary stereocentres α to a carbonyl group (Table 2; typical catalyst loading: 0.5–2.0 mol% nickel, corresponding to turnover numbers of ~40–160). A broad array of alkenylzirconium reagents serve as effective nucleophiles (Table 2, entries 1–17). Enantioconvergent carbon–carbon bond formation proceeds smoothly with alkyl substituents that range in steric demand from *n*-butyl to *t*-butyl (Table 2, entries 1–3). The alkenylzirconium reagent can bear a substituent other than an alkyl group, such as a silyl, alkenyl, aryl, or heteroaryl group (Table 2, entries 4–8). Good yields and enantioselectivities

are observed in the presence of a range of functional groups, including a thiophene, ether, silyl ether, ketone, primary alkyl chloride, primary alkyl bromide, and thioether (Table 2, entries 7–17).

The scope of the method with respect to the electrophilic coupling partner is also reasonably broad (Table 2, entries 18–37). In the case of α-bromo-γ-lactams, the catalyst provides quaternary stereocentres with good enantioselectivity with a variety of α-substituents (Table 2, entries 18–23). Furthermore, the substituent on the nitrogen of the γ-lactam can be aromatic (Table 2, entries 18–23) or aliphatic (Table 2, entries 24–26).

This method is not limited to the use of tertiary α-bromo-γ-lactams as the electrophilic coupling partner – the same nickel catalyst can achieve stereoconvergent substitution reactions of other cyclic α-halocarbonyl compounds to generate enantioenriched quaternary stereocentres (Table 2, entries 27–36). Thus, a variety of racemic α-halolactones (Table 2, entries 27–30) and α-haloketones (Table 2, entries 31–37) react with alkenylzirconium reagents to provide the desired products, including fluorinated compounds (Table 2, entries 36 and 37), with good yield and enantioselectivity. Lactones that bear α-quaternary stereocentres,[33] as well as carbonyl compounds with fully substituted α-stereocentres that include a trifluoromethyl or a fluorine substituent,[34,35] display an array of bioactivity; however, most enantioselective methods for the synthesis of organofluorine compounds are not catalytic and/or effective for tetrasubstituted stereocentres.[36–39]

Acyclic electrophiles.

Having established the viability of nickel-catalyzed enantioconvergent substitution reactions of cyclic tertiary electrophiles, we next turned our attention to achieving corresponding reactions of acyclic electrophiles. As has been noted in a recent review, substantially less progress has been described in the catalytic asymmetric synthesis of quaternary stereocentres when beginning with acyclic, rather than cyclic, starting materials.[4] Although we were not able to directly apply the method that we have developed for the alkenylation of racemic cyclic tertiary electrophiles (Table 2) to more conformationally flexible acyclic electrophiles, we have determined that, under modified conditions, a chiral nickel catalyst can indeed address the dual challenges of generating a quaternary carbon and controlling enantioselectivity (Table 4).

Thus, a nickel/bis(oxazoline) catalyst can achieve the enantioconvergent coupling of an array of racemic acyclic tertiary α-chloro-α-cyanoesters with alkenylzirconium reagents in good yield and enantiomeric excess (Table 4; for the impact of various reaction parameters on the yield and the enantioselectivity, see Table 3 and Supplementary Table 1); because these electrophiles are doubly activated, it is preferable to utilize more stable alkyl chlorides, rather than bromides. The scope with respect to the electrophile is reasonably broad. For example, the α-alkyl substituent can vary in steric demand from methyl to isobutyl (Table 4, entries 38–42), and it can bear functional groups such as an olefin, ether, silyl ether, acetal, ester, cyano group, primary alkyl fluoride, primary alkyl chloride, and imide (Table 4, entries 43–53). Furthermore, a range of esters, from methyl to t-butyl, serve as suitable coupling partners (Table 4, entries 54–57). Whereas removal of the cyano group can still lead to coupling with good yield and e.e. under our standard conditions (Table 4, entry 58),

our initial attempts at replacement of the carbonyl group have led to inefficient coupling (<35% yield). On a gram-scale (1.1 g of product), the coupling illustrated in entry 39 proceeds in 86% yield and 93% e.e..

With respect to the nucleophile, the scope of the method is also fairly broad (Table 4, entries 59–69). For example, good yields and enantioselectivities are observed with alkyl substituents on the alkenylzirconium reagent that vary in size from *n*-butyl to cyclohexyl (Table 4, entries 59–62). In the case of an unsaturated substituent, the coupling proceeds in modest yield with a 1-cyclohexenyl group (Table 4, entry 63), but in fair yield with a phenyl group (Table 4, entry 64). The alkenylzirconium nucleophile can include functional groups such as an ether, silyl ether, primary alkyl chloride, primary alkyl bromide, and thioether (Table 4, entries 65–69; for additional data, see Section V of the Supplementary Information).

Mechanistic observations.

With regard to mechanism, we hypothesize that, as for the nickel-catalyzed enantioconvergent reactions of secondary electrophiles that we have investigated,[40,41] these couplings of tertiary electrophiles proceed through a radical-chain pathway that includes the formation of an organic radical from the electrophile. As illustrated in Table 1 (entry 1 versus entry 14), we have observed that an alkyl bromide reacts significantly faster than the corresponding alkyl chloride, consistent with the possibility that loss of the halogen to form an organic radical may be turnover-limiting in the case of certain electrophiles.

The addition of TEMPO to a reaction inhibits carbon–carbon bond formation, which is consistent with the electrophile being converted into an organic radical under the coupling conditions. Furthermore, the coupling of an electrophile that bears an appropriately positioned olefin leads to cyclized product that is racemic, with virtually the same ratio of diastereomers as observed for the corresponding Bu_3SnH-mediated reductive cyclization, consistent with the formation of radical **A**, which cyclizes to **B** before proceeding to product (Figure 2). Thus, the enantioconvergence in these nickel-catalyzed couplings (Tables 2 and 4) is likely achieved via the formation of a radical intermediate from the electrophile, which is mechanistically distinct from nearly all previous catalytic asymmetric substitution reactions of tertiary electrophiles (Figure 1).

Applications of the coupling products.

To illustrate the synthetic utility of this new method for the catalytic enantioconvergent synthesis of quaternary stereocentres, we have transformed the products into a variety of other useful enantioenriched compounds, and we have applied them to the formal total synthesis of bioactive natural products (Figure 3). For example, in the case of a γ-lactam **6** (Figure 3a), deprotection of the PMP group furnishes an enantioenriched secondary γ-lactam (**70**), hydrogenation of the olefin provides α, α-dialkyl-γ-lactam (**71**), and reduction of the carbonyl group affords a pyrrolidine (**72**). Furthermore, an α-cyanoester **38** (Figure 3b) can be transformed into an enantioenriched carboxylic acid (**73**), primary alcohol (**74**), 1,3-dicarbonyl compound (**75**), and α,α-dialkyl-α-cyanoester (**76**).

With respect to the synthesis of natural products, the indole alkaloid (−)-eburnamonine has previously been generated from lactone **77**, which was prepared in five steps in 85% e.e., using a pyrrolidine as a chiral auxiliary (Figure 3c).[42] Beginning with a commercially available racemic 3-ethyloxolan-2-one, we have produced lactone **77** in four steps in 94% e.e., using asymmetric catalysis.

Furthermore, an enantioselective synthesis of madindoline A, an inhibitor of interleukin 6, has been described that proceeds via aldehyde **79**, which was generated in seven steps and 83% e.e. from the illustrated starting material through the use of an Evans chiral auxiliary (Figure 3d).[43] Utilizing our method, we have synthesized aldehyde **79** via asymmetric catalysis in five steps and 92% e.e..

Conclusion

A recent review has noted that two key challenges in the development of catalytic asymmetric methods for the synthesis of quaternary stereocentres are “the introduction of quaternary stereocentres in acyclic molecules” and the need to avoid “rare and/or expensive metals”.[4] In this study, we demonstrate that a catalyst based on nickel, an earth-abundant metal, enables the enantioconvergent substitution of both cyclic and acyclic racemic tertiary alkyl electrophiles (α-halocarbonyl compounds) with organometallic nucleophiles (alkenylzirconium reagents); the couplings proceed through a radical pathway, which distinguishes them from nearly all previous catalytic asymmetric substitution reactions of tertiary electrophiles. Carbon–carbon bond formation occurs under mild and convenient conditions (0 °C to room temperature) with noteworthy functional group compatibility, furnishing carbonyl compounds that bear an α-quaternary centre with good yield and enantioselectivity. The coupling products can be transformed into a variety of other useful families of compounds, and two of them have been applied to formal total syntheses of bioactive natural products, (−)-eburnamonine and madindoline A. Further efforts are underway to exploit the ability of transition-metal catalysts to generate radicals under mild conditions and to engage these intermediates in useful, enantioselective bond-forming reactions.

Methods

General procedure for the enantioconvergent alkenylations of cyclic tertiary electrophiles.

Preparation of the alkenylzirconium reagent: In the air, Cp_2ZrHCl (Schwartz’s reagent; 1.29 g, 5.0 mmol; moisture-sensitive, stored inside a glovebox) was quickly added to an oven-dried 20 mL vial equipped with a cross-shaped magnetic stir bar. The vial was then capped with a PTFE septum cap, and then it was evacuated and backfilled with nitrogen (three cycles). The vial was then attached to an argon-filled balloon, and anhydrous 1,4-dioxane (10.0 mL) was added via syringe, followed by the addition of the alkyne (5.0 mmol) via syringe in one portion. The reaction mixture was stirred vigorously at room temperature for 1–2 h, at which time all of the white solid had been consumed, and a homogeneous orange to dark-brown solution was observed. The concentration of the alkenylzirconium reagent was determined by titration with I_2 (~0.20 mmol) in anhydrous THF (2.0 mL); at the endpoint, the solution changes from dark-brown to bright yellow. The alkenylzirconium

solution was then cooled in an ice-water bath before use, under the protection of a nitrogen-filled balloon.

Preparation of a solution of the catalyst: In the air, $NiCl_2$·glyme (4.4 mg, 0.020 mmol) and chiral ligand **L1** (6.5 mg, 0.024 mmol) were added to an oven-dried 20 mL vial equipped with a cross-shaped magnetic stir bar. The vial was then capped with a PTFE septum cap and purged with an argon-filled balloon (21G needle in, and 21G needle out) for 5 min. Next, anhydrous 1,4-dioxane (10.0 mL) was added via syringe, and the mixture was vigorously stirred at room temperature under an argon-filled balloon for 30 min, furnishing a pale-yellow solution.

Enantioconvergent coupling: In the air, the electrophile (0.60 mmol, 1.0 equiv.) was added to an oven-dried 8 mL vial equipped with a magnetic stir bar. The vial was then capped with a PTFE septum cap and purged with an argon-filled balloon (21G needle in, and 21G needle out) for 5 min. Next, the solution of the catalyst (1.5 mL, 0.5 mol% catalyst loading) was added via syringe in one portion to the vial that contained the electrophile. The suspension was stirred at room temperature for 3 min, and then the solution of the alkenylzirconium reagent (0.72 mmol, 1.2 equiv.) was dropwise over 1 min. Next, the argon-filled balloon was removed, and the entire top of the septum cap was covered with vacuum grease. The reaction mixture was stirred at room temperature for 24 h.

Work-up: The reaction was quenched at room temperature through the addition of methanol (0.5 mL), followed by stirring for 5 min. Then, the reaction mixture was concentrated under reduced pressure and purified by flash chromatography on silica gel, which provided the desired coupling product.

General procedure for the enantioconvergent alkenylations of acyclic tertiary electrophiles.

Preparation of the alkenylzirconium reagent: In the air, Cp_2ZrHCl (Schwartz's reagent; 1.29 g, 5.0 mmol; moisture-sensitive, stored inside a glovebox) was quickly added to an oven-dried 20 mL vial equipped with a cross-shaped magnetic stir bar. The vial was then capped with a PTFE septum cap, and then it was evacuated and backfilled with nitrogen (three cycles). The vial was then attached to a nitrogen-filled balloon, and anhydrous 1,2-dimethoxyethane (DME, 10.0 mL) was added via syringe, followed by the addition of the alkyne (5.0 mmol) via syringe in one portion. The reaction mixture was stirred vigorously at room temperature for 1–2 h, at which time all of the white solid had been consumed, and a homogeneous orange to dark-brown solution was observed. The concentration of the alkenylzirconium reagent was determined by titration with I_2 (~0.20 mmol) in anhydrous THF (2.0 mL); at the endpoint, the solution changes from dark-brown to bright yellow. The alkenylzirconium solution was then cooled in an ice-water bath before use, under the protection of a nitrogen-filled balloon.

Preparation of a solution of the catalyst: In the air, $NiCl_2$·glyme (2.6 mg, 0.012 mmol, 2.0 mol%), chiral ligand **L2** (4.6 mg, 0.014 mmol, 2.4 mol%), and ZnF_2 (12 mg, 0.12 mmol, 0.20 equiv.) were added to an oven-dried 8 mL vial equipped with a cross-shaped

magnetic stir bar. The vial was capped with a PTFE septum cap, and then it was evacuated and backfilled with nitrogen (three cycles). The vial was next attached to a nitrogen-filled balloon, anhydrous 1,2-dimethoxyethane (1.2 mL) was added via syringe, and the suspension was stirred at room temperature for 30 min under a nitrogen-filled balloon.

Enantioconvergent coupling: In the air, the electrophile (0.60 mmol, 1.0 equiv.) was added in one portion to the solution of the catalyst at room temperature, and the resulting suspension was stirred at 0 °C in an *i*-PrOH bath for 10 min, followed by the dropwise addition over 1 min of the solution of the alkenylzirconium reagent (0.72 mmol, 1.2 equiv.). Next, the nitrogen-filled balloon was removed, and the entire top of the septum cap was covered with vacuum grease. The reaction mixture was stirred at 0 °C for 24 h.

Work-up: The reaction was quenched at 0 °C through the addition of methanol (0.5 mL), followed by stirring for 10 min. Then, the reaction mixture was concentrated under reduced pressure and purified by flash chromatography on silica gel, which provided the desired coupling product.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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References

1. Christoffers J & Baro A Quaternary Stereocenters: Challenges and Solutions for Organic Synthesis (Wiley–VCH, New York, 2005).
2. Das JP & Marek I Enantioselective synthesis of all-carbon quaternary stereogenic centers in acyclic systems. Chem. Commun 47, 4593–4623 (2011).
3. Li C, Ragab SS, Liu G & Tang W Enantioselective formation of quaternary carbon stereocenters in natural product synthesis: a recent update. Nat. Prod. Rep 37, 276–292 (2020). [PubMed: 31515549]
4. Quasdorf KW & Overman LE Catalytic enantioselective synthesis of quaternary carbon stereocentres. Nature 516, 181–191 (2014). [PubMed: 25503231]
5. Feng J, Holmes M & Krische MJ Acyclic quaternary carbon stereocenters via enantioselective transition metal catalysis. Chem. Rev 117, 12564–12580 (2017). [PubMed: 28910092]
6. Braun M & Kotter W Titanium(IV)-catalyzed dynamic kinetic asymmetric transformation of alcohols, silyl ethers, and acetals under carbon allylation. Angew. Chem. Int. Ed 43, 514–517 (2004).
7. Guo C, et al. Core-structure-oriented asymmetric organocatalytic substitution of 3-hydroxyoxindoles: application in the enantioselective total synthesis of (+)-folicanthine. Angew. Chem. Int. Ed 51, 1046–1050 (2012).
8. Zhao W, Wang Z, Chu B & Sun J Enantioselective formation of all-carbon quaternary stereocenters from indoles and tertiary alcohols bearing a directing group. Angew. Chem. Int. Ed 54, 1910–1913 (2015).

9. Wendlandt AE, Vangal P & Jacobsen EN Quaternary stereocentres via an enantioconvergent catalytic SN1 reaction. Nature 556, 447–451 (2018). [PubMed: 29695848]
10. Trost BM & Jiang C Atom economic asymmetric creation of quaternary carbon: regio- and enantioselective reactions of a vinylepoxide with a carbon nucleophile. J. Am. Chem. Soc 123, 12907–12908 (2001). [PubMed: 11749552]
11. Hou X-L & Sun N Construction of chiral quaternary carbon centers by Pd-catalyzed asymmetric allylic substitution with *P,N*-1,1′-ferrocene ligands. Org. Lett 6, 4399–4401 (2004). [PubMed: 15548035]
12. Zhang P, Le H, Kyne RE & Morken JP Enantioselective construction of all-carbon quaternary centers by branch-selective Pd-catalyzed allyl allyl cross-coupling. J. Am. Chem. Soc 133, 9716–9719 (2011). [PubMed: 21648464]
13. Khan A, Yang L, Xu J, Jin LY & Zhang YJ Palladium-catalyzed asymmetric decarboxylative cycloaddition of vinylethylene carbonates with Michael acceptors: construction of vicinal quaternary stereocenters. Angew. Chem. Int. Ed 53, 11257–11260 (2014).
14. Tsuchida K, Senda Y, Nakajima K & Nishibayashi Y Construction of chiral tri- and tetra-arylmethanes bearing quaternary carbon centers: copper-catalyzed enantioselective propargylation of indoles with propargylic esters. Angew. Chem. Int. Ed 55, 9728–9732 (2016).
15. Xu Y-W & Hu X-P Diastereo- and enantioselective copper-catalyzed decarboxylative ring-opening [3+2] annulation of tertiary propargylic carbamates through regioselective α-attack of γ-butenolides. Org. Lett 21, 8091–8096 (2019). [PubMed: 31553196]
16. Ma S, Han X, Krishnan S, Virgil SC & Stoltz BM Catalytic enantioselective stereoablative alkylation of 3-halooxindoles: facile access to oxindoles with C3 all-carbon quaternary stereocenters. Angew. Chem. Int. Ed 48, 8037–8041 (2009).
17. Zhang H, Hong L, Kang H & Wang R Construction of vicinal all-carbon quaternary stereocenters by catalytic asymmetric alkylation reaction of 3-bromooxindoles with 3-substituted indoles: total synthesis of (+)-perophoramidine. J. Am. Chem. Soc 135, 14098–14101 (2013). [PubMed: 24032694]
18. Zheng J, et al. Nickel-catalyzed conjugate addition of silyl ketene imines to in situ generated indol-2-ones: highly enantioselective construction of vicinal all-carbon quaternary stereocenters. Angew. Chem. Int. Ed 56, 13107–13111 (2017).
19. Liu X, et al. Construction of vicinal all-carbon quaternary stereocenters enabled by a catalytic asymmetric dearomatization reaction of β-naphthols with 3-bromooxindoles. ACS Catal. 8, 10888–10894 (2018).
20. Fu GC Transition-metal catalysis of nucleophilic substitution reactions: a radical alternative to SN1 and SN2 processes. ACS Cent. Sci 3, 692–700 (2017). [PubMed: 28776010]
21. Choi J & Fu GC Transition metal-catalyzed alkyl–alkyl bond formation: another dimension in cross-coupling chemistry. Science 356, eaaf7230 (2017). [PubMed: 28408546]
22. Iwasaki T & Kambe N Ni-catalyzed C–C couplings using alkyl electrophiles. Top. Curr. Chem 374, 66 (2016).
23. Kaga A & Chiba S Engaging radicals in transition metal-catalyzed cross-coupling with alkyl electrophiles: recent advances. ACS Catal. 7, 4697–4706 (2017).
24. Wang Z, Yin H & Fu GC Catalytic enantioconvergent coupling of secondary and tertiary electrophiles with olefins. Nature 563, 379–383 (2018). [PubMed: 30337711]
25. Li J, et al. Formal enantioconvergent substitution of alkyl halides via catalytic asymmetric photoredox radical coupling. Nat. Commun 9, 2445 (2018). [PubMed: 29934495]
26. Murakata M, Jono T, Mizuno Y & Hoshino O Construction of chiral quaternary carbon centers by catalytic enantioselective radical-mediated allylation of α-iodolactones using allyltributyltin in the presence of a chiral Lewis acid. J. Am. Chem. Soc 119, 11713–11714 (1997).
27. Wu L, Yang G & Zhang W Ni-catalyzed enantioconvergent coupling of epoxides with alkenylboronic acids: construction of oxindoles bearing quaternary carbons. CCS Chem. 1, 623–631 (2019).
28. Korch KM, Loskot SA & Stoltz BM Asymmetric synthesis of quaternary stereocenters via metal enolates. In PATAI'S Chemistry of Functional Groups; Rappoport Z. (Ed.), doi:10.1002/9780470682531.pat0858 (2017).

29. Minko Y & Marek I Stereodefined acyclic trisubstituted metal enolates towards the asymmetric formation of quaternary carbon stereocentres. Chem. Commun 50, 12597–12611 (2014).
30. Xu S, Kamada H, Kim EH, Oda A & Negishi E.-i. Pd-catalyzed cross-coupling with organometals containing Zn, Al, Zr, and so on – the Negishi coupling and its recent advances. In Metal-Catalyzed Cross-Coupling Reactions and More; De Meijere A & Brase S, Oestreich M (Eds.); Wiley–VCH, Weinheim, Germany, Vol. 1, 133–278 (2014).
31. Pandey G, Mishra A & Khamrai J Generation of all-carbon quaternary stereocenters at the C–3 carbon of piperidinones and pyrrolidinones and its application in natural product total synthesis. Tetrahedron 74, 4903–4915 (2018).
32. Lou S & Fu GC Enantioselective alkenylation via nickel-catalyzed cross-coupling with organozirconium reagents. J. Am. Chem. Soc 132, 5010–5011 (2010). [PubMed: 20302338]
33. Zhang L, et al. Bakkenolide A inhibits leukemia by regulation of HDAC3 and PI3K/Akt-related signaling pathways. Biomedicine & Pharmacotherapy 83, 958–966 (2016). [PubMed: 27522258]
34. Jennings LD, et al. Cyclobutane carboxamide inhibitors of fungal melanin: biosynthesis and their evaluation as fungicides. Bioorg. Med. Chem 8, 897–907 (2000). [PubMed: 10882002]
35. Saverino D, Debbia EA, Pesce A, Lepore AM & Schito GC Antibacterial profile of flurithromycin, a new macrolide. J. Antimicrob. Chemother 30, 261–272 (1992). [PubMed: 1452490]
36. Yang X, Wu T, Phipps RJ & Toste FD Advances in catalytic enantioselective fluorination, mono-, di-, and trifluoromethylation, and trifluoromethylthiolation reactions. Chem. Rev 115, 826–870 (2015). [PubMed: 25337896]
37. Bizet V, Besset T, Ma J-A & Cahard D Recent progress in asymmetric fluorination and trifluoromethylation reactions. Curr. Top. Med. Chem 14, 901–940 (2014). [PubMed: 24484424]
38. Fujiwara T & Takeuchi Y Application of chiral α-monofluorocarbonyl compounds to analytical and medicinal chemistry. Curr. Org. Chem 14, 950–961 (2010).
39. Zhu Y, et al. Modern approaches for asymmetric construction of carbon–fluorine quaternary stereogenic centers: synthetic challenges and pharmaceutical needs. Chem. Rev 118, 3887–3964 (2018). [PubMed: 29608052]
40. Schley ND & Fu GC Nickel-catalyzed Negishi arylations of propargylic bromides: a mechanistic investigation. J. Am. Chem. Soc 136, 16588–16593 (2014). [PubMed: 25402209]
41. Yin H & Fu GC A mechanistic investigation of enantioconvergent Kumada reactions of racemic α-bromoketones catalyzed by a nickel/bis(oxazoline) complex. J. Am. Chem. Soc 141, 15433–15440 (2019). [PubMed: 31502449]
42. Node M, Nagasawa H & Fuji K Chiral total synthesis of indole alkaloids of the *Aspidosperma* and *Hunteria* types. J. Org. Chem 55, 517–521 (1990).
43. Hosokawa S & Kobayashi S Total synthesis of madindoline A. J. Synth. Org. Chem., Jpn 59, 1103–1108 (2001).

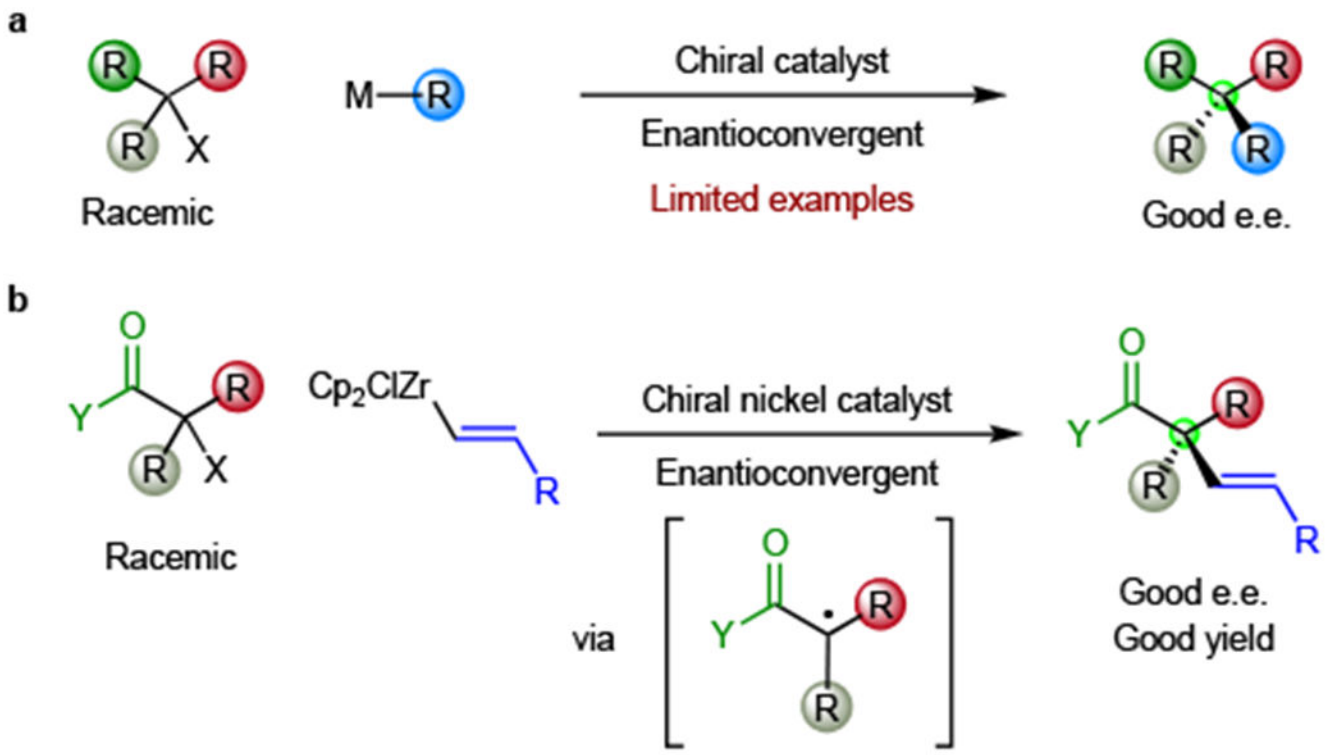


Fig. 1 |. Catalytic asymmetric synthesis of quaternary stereocentres via stereoconvergent nucleophilic substitution reactions of racemic tertiary alkyl electrophiles.

a, Previous approach: mainly focus on the heterolytic cleavage of the C–X bond with limited success. For the homolytic cleavage of the C–X bond, there is one catalytic example via Lewis acid catalysis[26], and one example via transition-metal catalysis[27]. **b**, Our approach: catalytic enantioconvergent alkenylation of tertiary α-halocarbonyl electrophiles via homolytic cleavage of the C–X bond. The advantages of this approach are: this method is effective for a variety of cyclic and acyclic tertiary electrophiles; we use mild conditions, with good functional group compatibility; and the turnover numbers are typically from ~40-160 (up to ~1600). Cp, cyclopentadienyl; M, metal; R, substituent; X, leaving group; Y, substituent.

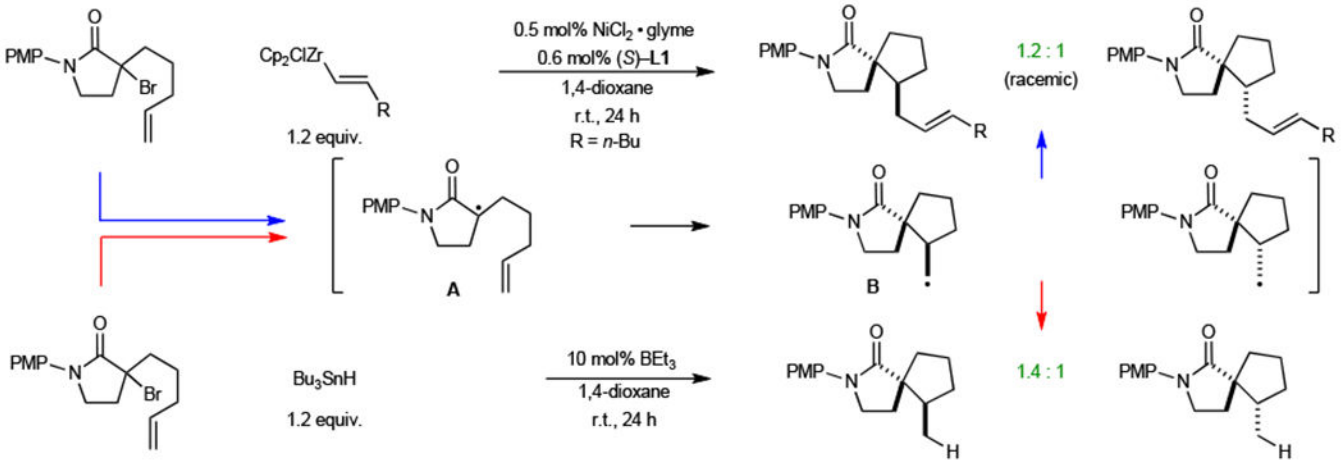


Fig. 2 |. Mechanistic studies.

The coupling of an electrophile with an appropriately positioned olefin provides cyclized product, which has virtually the same ratio of diastereomers as observed for the corresponding Bu_3SnH-mediated reductive cyclization, consistent with the formation of radical **A**, which cyclizes to **B** before proceeding to product. The result supports that these nickel-catalyzed couplings likely proceed via the formation of a radical intermediate from the electrophile.

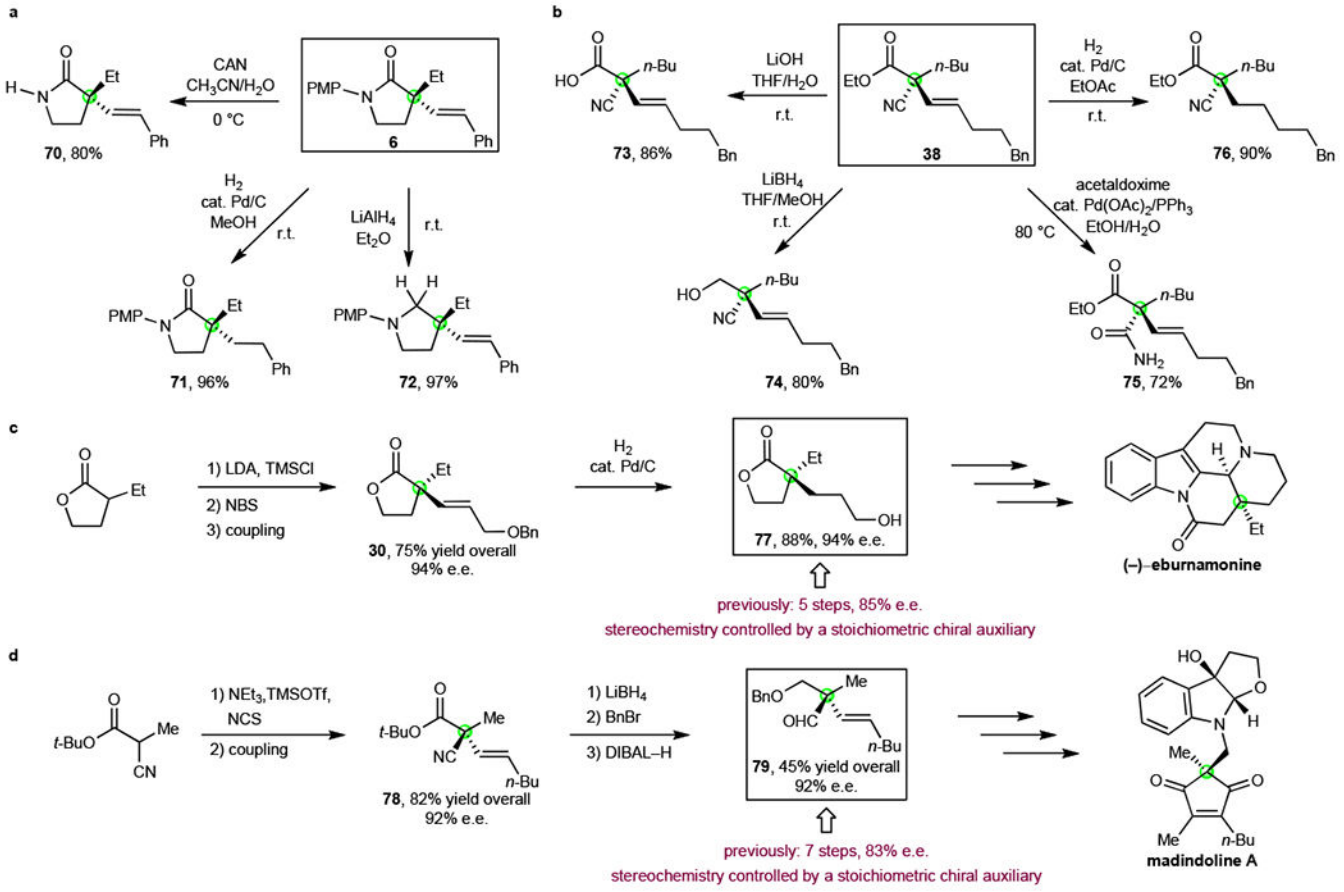
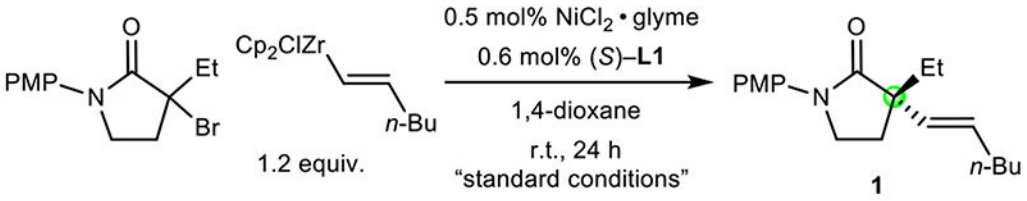


Fig. 3 |. Applications of the coupling products.

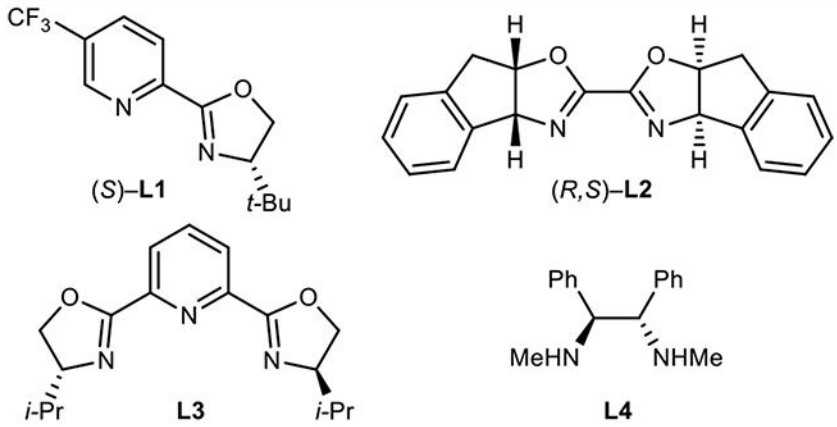
a, Product **6** is transformed to secondary γ-lactam **70**, α,α-dialkyl-γ-lactam **71**, and pyrrolidine **72**. **b**, Product **38** is transformed to carboxylic acid **73**, primary alcohol **74**, 1,3-dicarbonyl compound **75**, and α,α-dialkyl-α-cyanoester **76**. **c**, Lactone **77**, used in the total synthesis of (−)-eburnamonine,[42] is synthesized more efficiently with our method. **d**, Aldehyde **79**, used in the total synthesis of madindoline A,[43] is prepared more efficiently with our method. All reactions proceed without racemization of the quaternary stereocentre. CAN, ceric ammonium nitrate; DIBAL–H, diisobutylaluminum hydride; LDA, lithium diisopropylamide; NBS, *N*-bromosuccinimide; NCS, *N*-chlorosuccinimide; Tf, trifluoromethylsulfonyl.

Table 1.

Effect of reaction parameters on the nickel-catalyzed enantioconvergent substitution reaction of a tertiary cyclic electrophile.



entry	variation from the "standard conditions"	yield [%]	e.e. [%]
1	none	88	98
2	no $NiCl_2$ • glyme	<1	–
3	no **L1**	20	–
4	**L2**, instead of **L1**	36	27
5	**L3**, instead of **L1**	<1	–
6	**L4**, instead of **L1**	5	<5
7	1.0, instead of 1.2, equiv of the Zr reagent	78	98
8	12, instead of 24, h	82	98
9	0.05 equiv of H_2O added	76	98
10	1 mL of air, added via syringe	78	98
11	0.10 mol% $NiCl_2$ • glyme, 0.12 mol% **L1**	43	98
12	0.10 mol% $NiCl_2$ • glyme, 0.12 mol% **L1**, 5 days	76	98
13	0.025 mol% $NiCl_2$ • glyme, 0.030 mol% **L1**, 5 days	41	98
14	-Cl, instead of -Br, electrophile	4	98

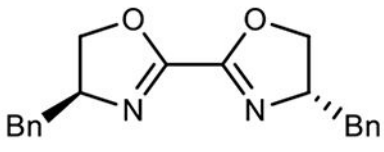


Reactions were conducted on a 0.2 mmol scale. All data are the average of two experiments; the yields were determined via GC analysis, with *n*-dodecane as an internal standard. *n*-Bu, *n*-butyl; *t*-Bu, *t*-butyl; *i*-Pr, *iso*-propyl; PMP, *para*-methoxyphenyl; r.t., room temperature.

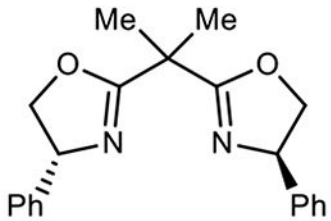
Table 2.

Effect of reaction parameters on the nickel-catalyzed enantioconvergent substitution reaction of a tertiary acyclic electrophile.

entry	variations from the "standard conditions"	yield [%]	e.e. [%]
1	none	92	94
2	no $NiCl_2$•glyme	<1	–
3	no **L2**	76	–
4	no ZnF_2	64	90
5	**L1**, instead of **L2**	26	–56
6	r.t., instead of 0 °C	80	90
7	1,4-dioxane, instead of DME	80	86
8	**L5**, instead of **L2**	80	–84
9	**L6**, instead of **L2**	5	–



L5

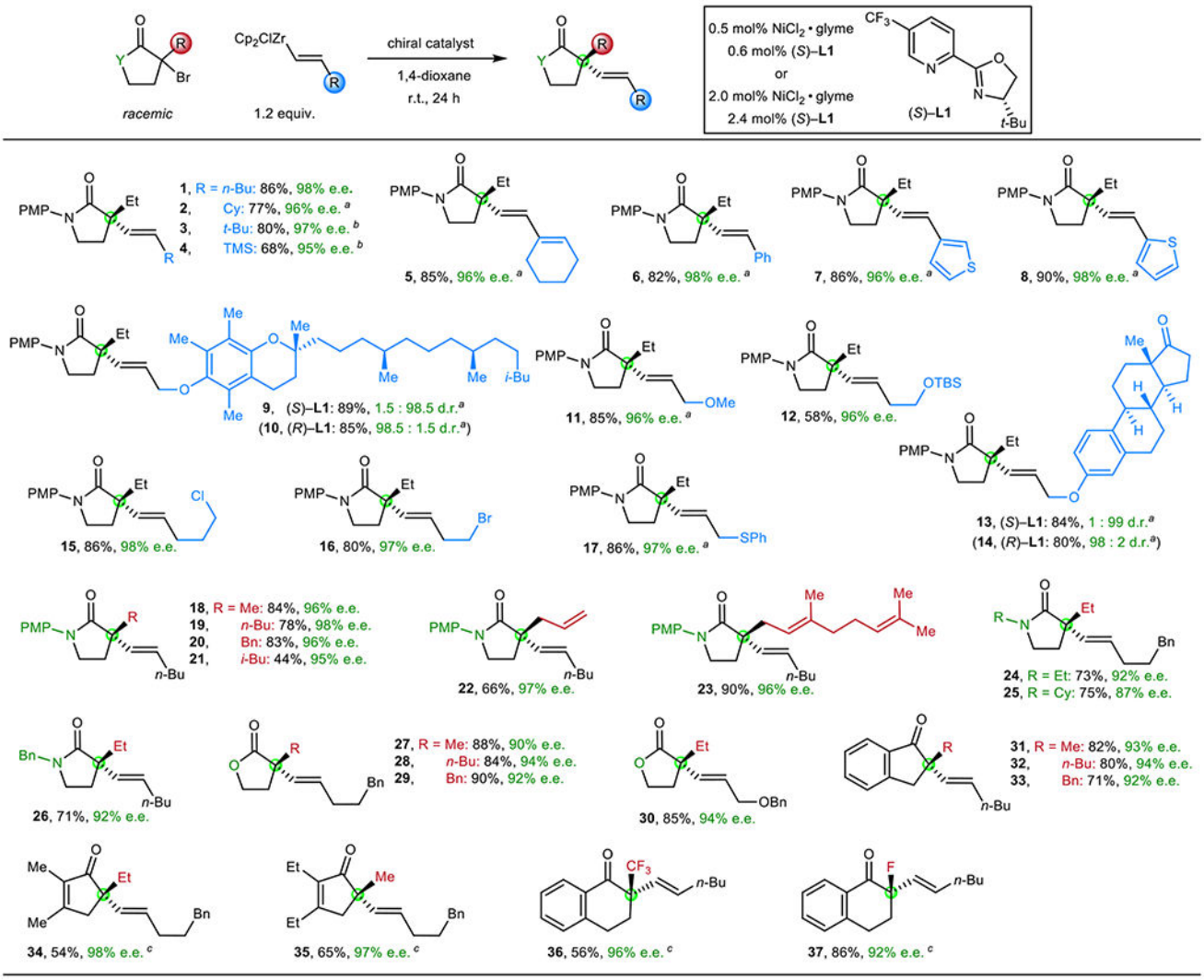


L6

Reactions were conducted on a 0.2 mmol scale. All data are the average of two experiments; the yields were determined via GC analysis, with *n*-dodecane as an internal standard. A negative e.e. value signifies that the other enantiomer of the product was formed predominantly. Bn, benzyl; DME, 1,2-dimethoxyethane.

Table 3.

Nickel-catalyzed enantioconvergent alkenylation of cyclic tertiary α-halocarbonyl compounds.



Reactions were conducted on a 0.6 mmol scale. Yields were determined after column chromatography.

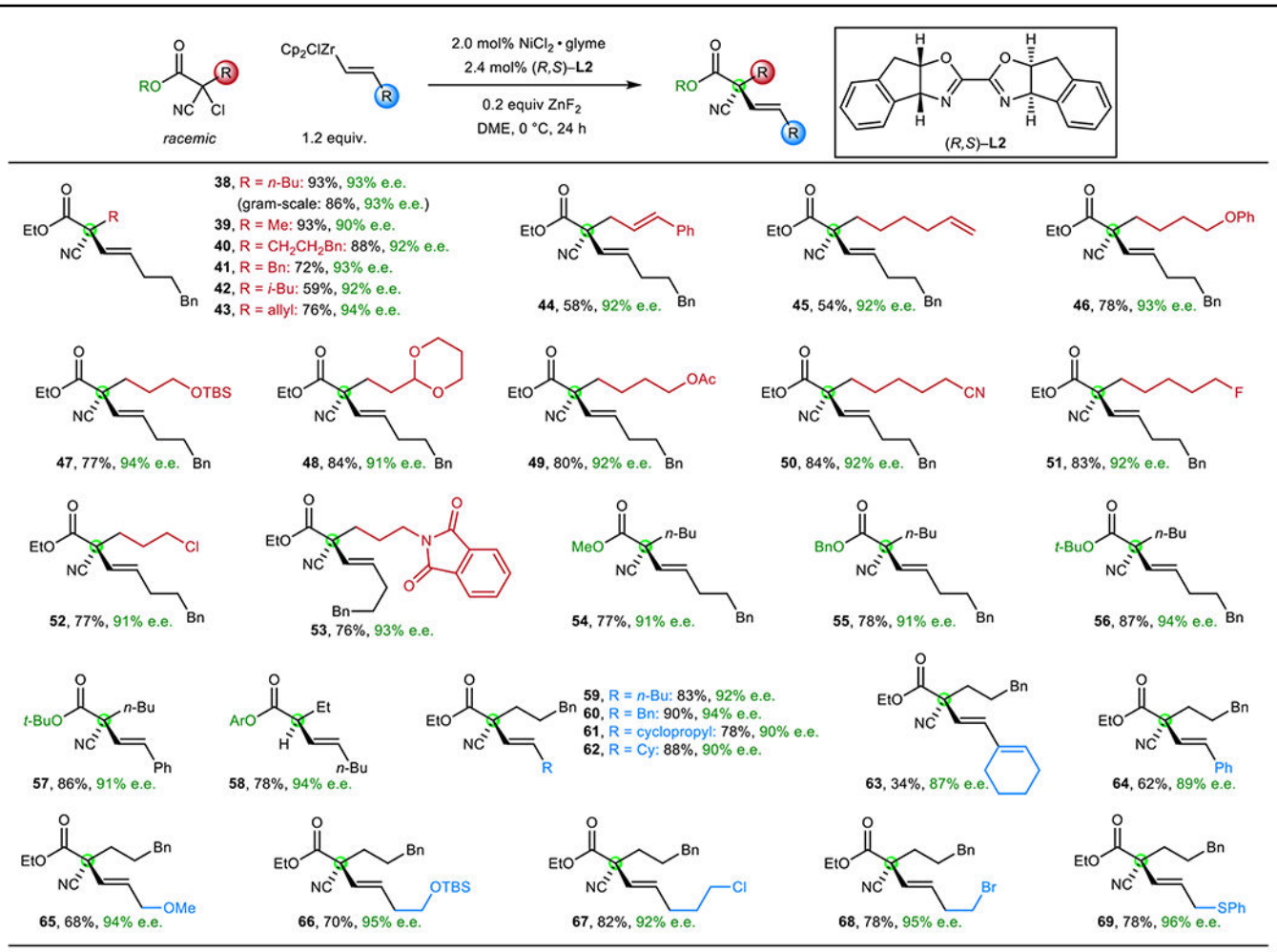
[a] 2.0 mol% $NiCl_2$·glyme, 2.4 mol% (*S*)-**L1**;

[b] 7.0 mol% $NiCl_2$·glyme, 8.4 mol% (*S*)-**L1**;

[c] Cl as the leaving group. TBS, *tert*-butyldimethylsilyl; TMS, trimethylsilyl. r.t., room temperature; d.r., diastereomeric ratio; e.e., enantiomeric excess.

Table 4.

Nickel-catalyzed enantioconvergent alkenylation of acyclic tertiary α-halocarbonyl compounds.



Reactions were conducted on a 0.6 mmol scale. Yields were determined after column chromatography. Ac, acetyl; ArO, 2,6-di-*t*-butyl-4-methylphenol.